Early Enteral Feeding, Compared With Parenteral, Reduces Postoperative Septic Complications

The Results of a Meta-Analysis

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This two-part meta-analysis combined data from eight prospective randomized trials designed to compare the nutritional efficacy of early enteral (TEN) and parenteral (TPN) nutrition in high-risk surgical patients. The combined data gave sufficient patient numbers (TEN, n = 118; TPN, n = 112) to adequately address whether route of substrate delivery affected septic complication incidence. Phase I (dropouts excluded) meta-analysis confirmed data homogeneity across study sites, that TEN and TPN groups were comparable, and that significantly fewer TEN patients experienced septic complications (TEN, 18%; TPN, 35%; p = 0.01). Phase II meta-analysis, an intent-to-treat analysis (dropouts included), confirmed that fewer TEN patients developed septic complications. Further breakdown by patient type showed that all trauma and blunt trauma subgroups had the most significant reduction in septic complications when fed enterally. In conclusion, this meta-analysis attests to the feasibility of early postoperative TEN in high-risk surgical patients and that these patients have reduced septic morbidity rates compared with those administered TPN.

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THERE IS AN EMERGING consensus that early postoperative nutritional support benefits the high-risk surgical patient by decreasing septic morbidity, maintaining immunocompetence, and improving wound healing.[1-8] The optimal route of substrate delivery (enteral *versus* parenteral), however, continues to be debated.[9-16] Safety, convenience, and cost have been traditional arguments favoring the enteral route; but fear of gastrointestinal (GI) intolerance has discouraged its use in the postoperative stressed patient.[17] Now, however, basic and clinical research offer compelling physiologic benefits of enteral feeding. Substrates delivered by the enteral route are better utilized by the gut than those administered parenterally.[16,18-20] Additionally, total enteral nutrition (TEN), when compared with current total parenteral nutrition (TPN) solutions, prevents gastrointestinal mucosal atrophy, attenuates the injury stress response, maintains immunocompetence, and preserves normal gut flora.[13-15,21-27] Despite these considerations, there are few prospective, randomized, controlled trials (PRCTs) comparing TEN with TPN in high-risk surgical patients, and the available studies lack the sample size necessary to document whether TEN, by maintaining gut function, improves clinical outcome.[9-11,16,28,29] A large multicenter trial designed to answer this specific question could provide results at some future time but would be time consuming as well as costly. Meta-analysis, a systematic method of combining data from multiple studies, is an effective option to derive practical therapeutic extrapolations now from results of already completed PRCTs.[30,31]

Eight similar PRCTs of small size were conducted to determine the nutritional equivalence between early postoperative TEN and TPN in various high-risk surgical patient populations that by convention have been fed parenterally. Two of these trials are published; both attest to patient tolerance of early postoperative enteral feeding.[9,11] One trial demonstrated a significant reduction in major septic complications in those patients receiving early post-injury TEN.[9] Review of the six unpublished

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TABLE 1. *Criteria for Meta-analysis Inclusion Eligibility*

Inclusion Criteria	Exclusion Criteria
Initiation of nutritional support within 72 postoperative hr	Preexisting diseases, including advanced diabetes, chronic renal failure, cirrhosis, and inflammatory bowel disease
Vivonex TEN or study TPN solution as initial postoperative feeding	Conditions precluding use of TEN (*e.g.*, bowel obstruction)
Moderately to severely stressed (*i.e.*, high-risk surgical) patients	Severe head injury (Glasgow Coma Scale ≤5)
Daily documentation of postoperative complications	Any reason for preclusion of aggressive nutritional support (*e.g.*, low flow state)
	Hospitalization of ≥10 days before study enrollment
	Prior surgical procedures during study enrollment hospital stay
	Preoperative nutritional support
	Nonstudy nutritional solution used immediately after operation

TEN, total enteral nutrition; TPN, total parenteral nutrition.

PRCTs showed a similar trend toward decreased sepsis. The purpose of this study, therefore, was to apply meta-analysis to the data from these eight PRCTs to ascertain whether early TEN, when compared with TPN, was associated with fewer septic complications.

Materials and Methods

Eight PRCTs conducted during a 4-year period ending June 1988 met criteria for inclusion in this meta-analysis (Table 1). The study protocols were approved by each site's Institutional Review Board, and informed consent was obtained from each patient. These studies were conducted to compare the utility of Vivonex T.E.N. (Norwich Eaton Pharmaceuticals, Inc., Norwich, NY) with nutritionally similar TPN solutions in moderately to severely stressed postoperative patients. A literature review showed that no other published trials met the inclusion criteria for this meta-analysis. The eight studies contributing data enrolled 230 patients (19 to 59 patients each); 118 were randomized to receive TEN, and 112 were randomized to receive TPN. Four studies enrolled only trauma patients with an Abdominal Trauma Index (ATI) of 15 to 40 or an Injury Severity Score (ISS) of 9 to 40. The remaining four studies enrolled trauma or other surgical patients who would normally require postoperative nutritional support.

Nutritional Formulas

Patients received TEN by tube/needle catheter jejunostomy (n = 81), nasoenteric tube (n = 36), or gastrojejunal tube (n = 1). All enterally fed patients received Vivonex T.E.N. The TPN solutions (Table 2) used in seven studies were designed to be comparable in composition to TEN and were prepared by hospital pharmacies. The remaining study site employed a standard glucose-based TPN solution using Freamine III (Kendall-McGaw Laboratories, Inc., Irvine, CA) as the amino acid source.[11]

Study Design

Time of initiating nutritional support was site dependent and varied from 8 to 72 hours after operation. Total enteral nutrition was started at one-quarter strength (0.25 Kcal/mL) or one-half strength (0.50 Kcal/mL) at a rate of 50 mL/hour. Patients were closely observed for GI intolerance while rate and then concentration were advanced to deliver the targeted nutritional goal (0.20 to 0.25 g N/kg body weight/day) within 72 hours. Total par-

TABLE 2. *Nutritional Support Solutions: Macronutrient Content per Liter*

		Parenteral Formulas		
	Enteral Formula Vivonex TEN (all sites)	6.9% Freamine HBC and 6.0 Trophamine* (4 sites)	10% Travasol and 4% Branchamine† (3 sites)	Freamine III* (1 site)
Calories	1000	1174	1139	1031
Amino acids (g)	38	38	38	36
Per cent BCAA	33.1	35.6	32.5	23.3
EAA:NEAA ratio	1:1	1:1	1:1	1:1
Per cent glutamine	12.9	0	0	0
Carbohydrates (g)	206	242	240	214
Lipid (g)	3	6‡	3‡	3.4‡
NPC:N	149:1	156:1	156:1	147:1

* Kendall-McGaw Laboratories, Inc., Irvine, CA. † Travenol Laboratories, Deerfield, IL. ‡ Intralipid (KabiVitrum, Franklin, OH).

BCAA, branched chain amino acids; EAA, essential amino acids; NEAA, nonessential amino acids; NPC:N, nonprotein calorie to nitrogen ratio.

enteral nutrition was to be delivered in an isonitrogenous manner at five sites; the remaining sites advanced TPN more rapidly than the TEN protocol. Dropouts were defined by early study withdrawal (<72 hrs) due to non–diet-related issues (*e.g.*, relaparotomy, transfer to another hospital, death, and so forth). Treatment failures were defined by diet-related problems (*e.g.*, nutritional access complications, severe GI intolerance, or metabolic problems) that precluded achievement of nutritional goals.

Urine for nitrogen balance and venous blood for biochemical analyses were obtained at baseline (day 0 or 1), midstudy (day 4, 5, or 6) and end of study (day 7, 8, or 9). All sites performed the following laboratory tests: complete blood count with differential, platelet count, electrolytes, liver function tests (lactate dehydrogenase, alkaline phosphatase, total bilirubin, serum glutamic-oxaloacetic transaminase), total protein, albumin, and transferrin. Additionally, baseline demographics were recorded, daily nutritional assessments were performed, and a variety of outcome variables were tracked. Variables recorded by all sites included nonseptic and septic complications, GI intolerance, number of days to regular diet, number of days in intensive care (ICU), and length of hospital stay. Complications were prospectively recorded. No prospective criteria were established for the diagnosis of specific complications, and diagnoses were made by each investigator based on conventional clinical criteria. This was a two-part meta-analysis. In the phase I meta-analysis (described below), complication data were extracted from study patient case report forms. Based on highly significant differences in septic complications between the TEN and TPN treatment groups in the first analysis, a second analysis was conducted to rigorously evaluate septic complication differences. A retrospective review of patient charts ensued to ensure that complications in the database and source documents were in agreement as well as to acquire morbidity and mortality data not previously collected on study dropouts. A physician reviewer, blinded to treatment, retrospectively categorized specific complications as (1) septic or (2) nonseptic or indeterminable.

Statistical Methods

Each meta-analysis had a statistical protocol in place before its conduct. In phase I, summary statistics (*i.e.*, mean ± standard deviation) were evaluated for each treatment group from the eight study sites, and dropouts were excluded. In phase II, individual patient data were used to permit comparisons among five patient subgroups, and dropouts were included. In phase I and phase II meta-analyses, statistical significance was reported at $p < 0.05$.

Variables evaluated in phase I included (1) diet intake and nutritional responses (*e.g.*, nitrogen balance); (2) change in body weight; (3) time to start of nutritional support; (4) biochemical responses (*e.g.*, total protein); (5) GI intolerance; (6) postoperative complications; and (7) length of time in hospital, ICU, and cost of hospitalization.

Preliminary tests were performed to identify outliers (Grubb's procedure), to assess homogeneity of variance across studies and treatments (on two-way ANOVA on natural logarithms), and to determine treatment-by-study interactions (two-factor ANOVA).[32] Separate variance estimates were employed within studies or within studies and treatments if the assumption of variance homogeneity was violated. If treatment-by-study interactions were nonsignificant, pooled estimates of treatment differences for quantitative variables (*e.g.*, nitrogen balance) were calculated by (weighted) averaging within-study treatment differences. Least squares means were calculated for each treatment group as simple, unweighted averages across studies of the within-treatment effects. For significant treatment-by-study interactions, responses were reanalyzed after adjusting for potential explanatory variables in the ANOVA models, on a case-by-case basis.

For categorical variables (*e.g.*, postoperative complications, race, sex, and so forth), response rates and pooled estimates of average treatment differences were determined by logistic regression analysis using PROC CATMOD, an SAS (Cary, NC) procedure that performs a nonparametric categorical modeling of data analogous to ANOVA and general linear model (GLM).[33] Treatment differences were tested also by stratified contingency table tests, with individual studies as strata, using the Cochran-Mantel-Haenszel test. The pooled Cochran-Mantel-Haenszel statistic combines within-study comparisons of treatment groups.[34] Sensitivity of the eight combined studies to detect clinically important differences between treatment groups was assessed by after-the-fact power calculations. These were based on results of the additive ANOVA or logistic regression analyses of treatment group effects for quantitative or categorical responses, respectively.

Phase II was an intent-to-treat analysis (*i.e.*, dropouts were included), and individual patient data were used to permit comparisons of five patient subgroups: all patients, all trauma patients, penetrating trauma patients, blunt trauma patients, and all nontrauma patients. Variables evaluated were days in hospital and ICU; 10-day complication rates and types of complications; and 10- and 30-day mortality rates. Analysis of variance was used to compare quantitative responses; stratified contingency table analysis was used to compare categorical variables. Unweighted two-way ANOVA was performed on continuous baseline responses to determine differences between treatments. As in the phase I meta-analysis, ANOVA models included treatment, site, and treatment-by-site interactions. Preliminary tests were performed (*e.g.*, to

TABLE 3. *Patient Breakdown by Study Site, Route of Nutrition, and Patient Type: Phase II (Phase I)* Data*

Study Site	Route	Total Patients	Blunt Trauma Patients	Penetrating Trauma Patients	Nontrauma Patients
Ben Taub General Hospital, Houston, TX	TEN	12 (11)	0 (0)	12 (11)	0 (0)
	TPN	11 (11)	0 (0)	11 (11)	0 (0)
Buffalo General, Buffalo, NY	TEN	9 (9)	2 (2)	2 (2)	5 (5)
	TPN	10 (10)	2 (2)	3 (3)	5 (5)
Cincinnati University, Cincinnati, OH	TEN	13 (11)	0 (0)	0 (0)	13 (11)
	TPN	11 (11)	0 (0)	0 (0)	11 (11)
Denver General, Denver, CO	TEN	29 (21)	13 (8)	16 (13)	0 (0)
	TPN	30 (25)	10 (8)	20 (17)	0 (0)
Good Samaritan, Cincinnati, OH	TEN	10 (6)	0 (0)	0 (0)	10 (6)
	TPN	10 (10)	0 (0)	0 (0)	10 (10)
Medical College of Virginia, Richmond, VA	TEN	12 (11)	7 (6)	5 (5)	0 (0)
	TPN	10 (10)	6 (6)	4 (4)	0 (0)
Montreal General, Montreal, Quebec	TEN	11 (9)	7 (5)	0 (0)	4 (4)
	TPN	10 (9)	8 (7)	0 (0)	2 (2)
University of Texas, Houston, TX	TEN	22 (14)	19 (13)	3 (1)	0 (0)
	TPN	20 (16)	18 (14)	2 (2)	0 (0)
All studies	TEN	118 (92)	48 (34)	38 (32)	32 (26)
	TPN	112 (102)	44 (37)	40 (37)	28 (28)

* Phase I meta-analysis excludes dropouts.

TEN, total enteral nutrition; TPN, total parenteral nutrition.

identify outliers). A weighted two-way ANOVA without the treatment-by-study interaction was performed for the time interval response time in hospital and time in ICU, both with and without outliers. Each subgroup weight was based on the standard deviation for each treatment and study combination, using all patients. The critical values for the F-test were based on an assumption of 13 degrees of freedom for the denominator mean square in the F-ratio, which was based on the average sample size (14.4) within each study and treatment combination. For categorical responses, Fisher's exact test and the Cochran-Mantel-Haenzel test were used to determine whether significant associations existed between treatment group and presence of categorical responses.

Results

Phase I meta-analysis assessed 194 (92 TEN, 102 TPN) patients, including treatment failures and excluding study dropouts. Patient enrollment, by study site, route of nutrition, and patient type are shown in Table 3. The phase II meta-analysis analyzed all 230 patients on an intent-to-treat basis. Patients were equally distributed between groups in terms of nontrauma surgery; these procedures are summarized in Table 4 and included 18 emergencies, 14 cancer operations, and 28 nontumor nontrauma procedures.

The phase I meta-analysis demonstrated that the combined treatment groups (TEN *versus* TPN) were comparable with regard to age, sex, race, injury/surgery type, and initial level of stress (ATI, ISS, basal energy expenditure, urinary nitrogen) despite intersite demographic differences (Table 5). The Phase II meta-analysis of subgroups demonstrated that (1) the two treatment groups were similar when further subdivided by patient type (all trauma, blunt trauma, penetrating trauma, nontrauma surgery) for age, race, injury/surgery type, and ISS; (2) basal energy expenditure, urinary nitrogen, and time to start of feeding were similar between the two groups; (3) significantly more men were randomized to the TPN nontrauma subgroup; and (4) a significantly greater mean ATI for the TPN penetrating trauma subgroup (TEN, 23.8 $\pm$ 1.7; TPN, 30.2 $\pm$ 2.2; $p < 0.05$).

In the penetrating trauma subgroup, patients randomized to the TPN group had a significantly greater mean

TABLE 4. *Nontrauma Operations for TEN and TPN Study Groups*

Anatomic Site	TEN (n = 32)	TPN (n = 28)
Stomach		
Resection	6	3
Vagotomy and drainage, Graham closure, etc.	3	5
Pancreas		
Resection	2	4
Drainage	1	4
Complex biliary		
Sphincteroplasty	3	1
Drainage	3	1
Colectomy	4	3
Cardiac procedures	4	2
Esophagectomy	2	0
Hepatectomy	1	0
Vascular	1	1
Other*	2	4

* Includes exploratory laparotomy for metastatic carcinoma, total cystectomy, oophorectomy, radical nephrectomy, duodenotomy, and duodenojejunostomy.

TEN, total enteral nutrition; TPN, total parenteral nutrition.

TABLE 5. *Homogeneity of TEN and TPN Study Groups*

	TEN (n = 92)	TPN (n = 102)	P
Age (yr)*	41.0 ± 1.5	41.8 ± 1.5	NS
Race (%)			
White	57	53	NS
Black	27	27	NS
Other	16	20	NS
Sex (%)			
M	68	77	NS
Injury type			
Blunt (n)	34	37	
Penetrating (n)	32	37	
Nontrauma (n)	26	28	
BEE (kcal)*	1666 ± 29	1651 ± 27	NS
UN (g/dL)*	13.3 ± 0.8	12.5 ± 0.8	NS
ATI*†	24.5 ± 1.7	23.3 ± 1.7	NS
ISS*†	26.7 ± 1.7	26.3 ± 1.4	NS

* Mean ± SEM.

† Phase II data: ATI includes 61 (37 penetrating, 24 blunt) TEN and 63 (38 penetrating, 25 blunt) TPN patients; ISS includes 65 (27 penetrating, 38 blunt) TEN and 64 (27 penetrating, 27 blunt) TPN patients.

TEN, total enteral nutrition; TPN, total parenteral nutrition; BEE, basal energy expenditure; UN, urinary nitrogen; ATI, abdominal trauma index; ISS, injury severity score.

ATI than did patients who were randomized to the TEN group (TEN, 23.8 ± 1.7; TPN, 30 ± 2.2; p = 0.025); however, ISS were not significantly different (TEN, 22.6 ± 2.7; TPN, 25.8 ± 2.3; p = 0.36). In the blunt trauma subgroup, neither ATI (TEN, 24.2 ± 2.1; TPN, 19.4 ± 2.1; p = 0.17) nor ISS (TEN, 30.5 ± 2.2; TPN, 29.3 ± 2.1; p = 0.69) were significantly different. In the all trauma (penetrating and blunt) subgroup, ATI (TEN, 24.5 ± 1.7, TPN, 23.3 ± 1.7; p = 0.61) and ISS (TEN, 28.1 ± 1.9; TPN, 28.4 ± 1.6; p = 0.91) were comparable.

Thirty-six patients were classified as dropouts for non-diet-related reasons including protocol violations (10 TEN, 3 TPN), patient/primary MD preference (8 TEN, 1 TPN), reoperation within 72 hours (4 TEN, 2 TPN), death within 72 hours (2 TEN, 3 TPN), and other miscellaneous reasons (2 TEN, 1 TPN). The TEN group had significantly more study dropouts (TEN = 26, TPN = 10; p = 0.001). Of the 92 completed TEN patients, 15 (16%) were classified as treatment failures because of GI intolerance (distention/cramping in eight, high gastric residuals in six, and diarrhea in one). Nine of the 15 TEN treatment failures had sustained blunt trauma, five had penetrating injuries, and one had undergone a nontrauma surgical procedure. Of the 102 TPN patients, treatment failed in three (3%) because of metabolic problems (hyperglycemia in two, ascites in one). All three TPN treatment failures had blunt injuries. The difference in number of TEN and TPN treatment failures was statistically significant (p = 0.001).

Phase I

The time to start postoperative nutritional support did not significantly differ between the two treatment groups (TEN, 32.5 ± 1.8 hours; TPN, 32.8 ± 1.7 hours; p = not significant). Although baseline, midstudy, and end-of-study nitrogen intake and nitrogen balance were significantly less in the TEN group, the difference in nitrogen balance between the two groups narrowed over time (Fig. 1). There were two significant treatment-by-site interactions for two end points. Baseline nitrogen intake was higher at two sites because TPN was advanced more rapidly than at the remaining six sites. At one site, the TEN patients had significantly greater initial nitrogen output than did the TPN patients. Weight gain by end of study was significantly less in the TEN group (difference, 1.6 kg; p = 0.03). Both groups advanced from study diet to a regular diet in approximately 11 days. Biochemical data are displayed in Figure 2 and Table 6. There were no significant differences in baseline values, with the exception of lower glucose levels in the TEN group. Glucose

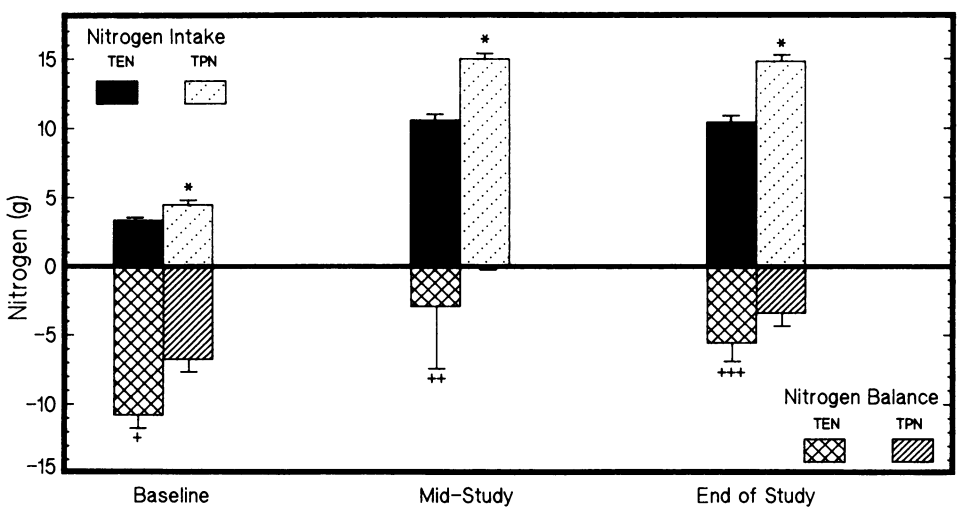

FIG. 1. Nitrogen balance. Nitrogen intake: TEN, ■; TPN, ⚃. *p < 0.001. Nitrogen balance: TEN, ▩; TPN, ▨. †p < 0.001; ††p < 0.005; †††p < 0.05.

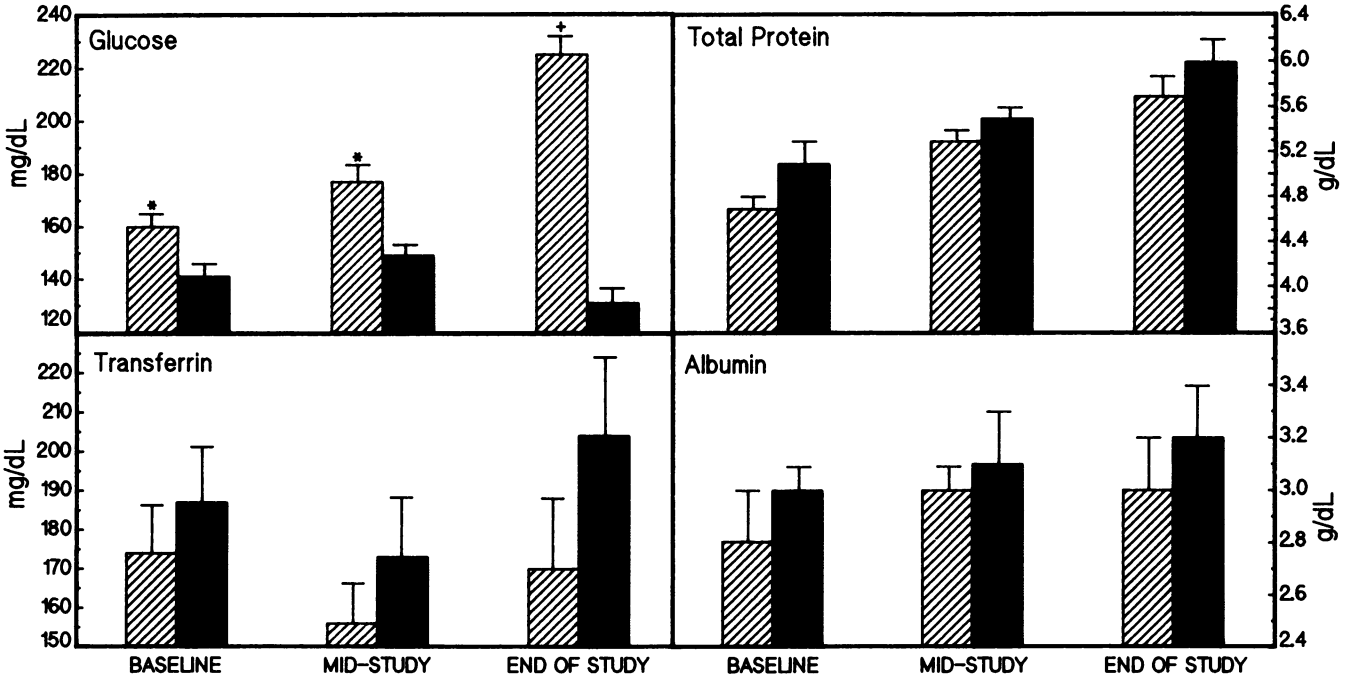

FIG. 2. Selected biochemical values for TEN and TPN groups (phase I). TEN, ■; TPN, ▨. *$p < 0.05$; †$p < 0.001$.

levels remained significantly lower in the TEN group, and differences increased throughout the study period (19 mg/dL at baseline, $p = 0.02$; 28 mg/dL at midstudy, $p = 0.03$; and 94 mg/dL at end of study, $p = 0.0001$). Significantly lower midstudy serum glutamic oxalo-acetic transaminase ($p = 0.05$), midstudy lactate dehydrogenase ($p = 0.002$), and end-of-study lactate dehydrogenase ($p = 0.006$) levels were noted in the TEN group. End-of-study nutritional markers (total protein, albumin, and transferrin) were slightly higher in the TEN group (p = not significant).

Gastrointestinal intolerance and postoperative complications were evaluated separately. Overall, GI discom-

TABLE 6. *Laboratory Values of TEN and TPN Study Groups (Phase I Meta-analysis)*

	TEN	TPN	P
Leukocytes ($\times 10^3$/L)			
Baseline	1333 ± 637 (79)	1284 ± 602 (89)	0.06
End of study	1362 ± 676 (77)	1548 ± 698 (76)	NS
TLC ($\times 10^3$/L)			
Baseline	1666 ± 161 (88)	1595 ± 153 (98)	NS
End of study	1640 ± 151 (81)	1746 ± 147 (87)	NS
Total bilirubin (mg/dL)			
Baseline	1.2 ± 0.2 (90)	0.9 ± 5.0 (96)	NS
Mid-study	1.2 ± 0.2 (88)	1.5 ± 0.2 (99)	NS
End of study	1.5 ± 0.3 (61)	2.0 ± 0.2 (76)	NS
LDH (U/dL)			
Baseline	389 ± 28 (53)	421 ± 32 (56)	NS
Mid-study	285 ± 12 (50)	390 ± 23 (58)	0.002
End of study	309 ± 17 (45)	385 ± 24 (58)	0.006
SGOT (U/dL)			
Baseline	107 ± 10 (92)	103 ± 10 (97)	NS
Mid-study	56 ± 3 (87)	67 ± 4 (99)	0.05
End of study	53 ± 3 (63)	62 ± 4 (75)	NS
Alkaline phosphatase (U/dL)			
Baseline	66 ± 3 (91)	63 ± 3 (96)	NS
Mid-study	79 ± 4 (87)	81 ± 4 (99)	NS
End of study	127 ± 8 (62)	136 ± 7 (74)	NS

Mean ± SEM (n).
TLC, total lymphocyte count; LDH, lactic acid dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase.

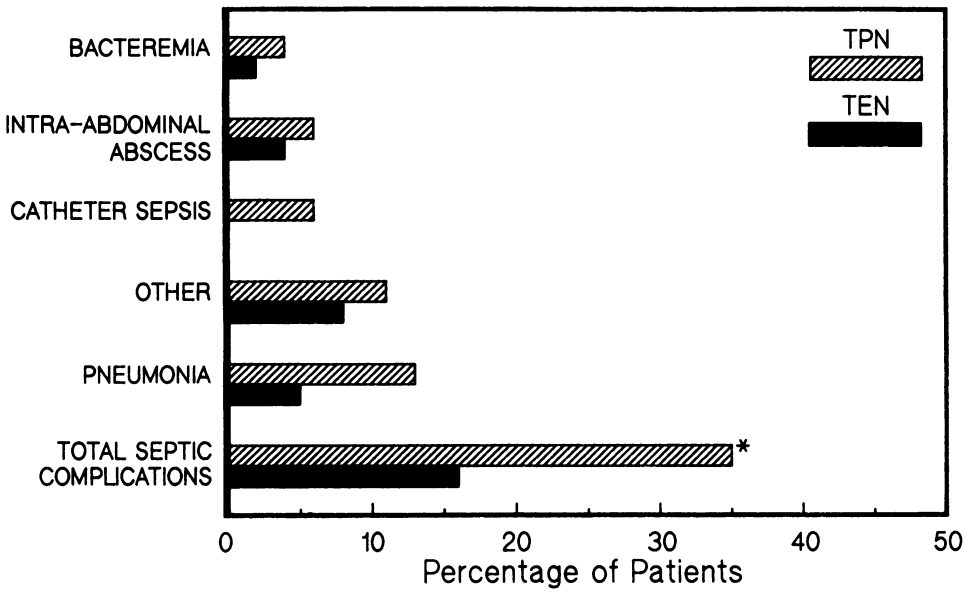

FIG. 3. Postoperative septic complications (phase II). *p < 0.05.

fort was significantly greater with enteral feeding. Twice as many TEN patients experienced abdominal distention (TEN, 46%; TPN, 24%; p = 0.003); distention was graded as moderate to severe in 14% of TEN patients compared with 4% of TPN patients (p = 0.001). More TEN patients had diarrhea (TEN, 34%; TPN, 9%; p = 0.001), which was graded as moderate to severe in 13% of TEN *versus* 4% of TPN patients (p = 0.03). Significantly fewer TEN patients experienced total complications (TEN, 38%; TPN, 59%; p = 0.007) and septic complications (TEN, 17%; TPN, 44%; p = 0.0001). After-the-fact power calculations indicated that analyses of the combined data from these eight studies were able to detect differences between groups with high sensitivity. Differences in rates of GI intolerance and complications were detectable at the p = 0.05 significance level with power in excess of 80%.

Phase II

A total of 81 septic and nonseptic/indeterminable postoperative complications occurred in 48 (41%) TEN patients compared with 91 such complications in 58 (52%) TPN patients (p = 0.09). Nonseptic/indeterminable complications were equally distributed between the two treatment groups, and this was true for each patient type subgroup (all trauma, blunt trauma, etc.). Figure 3 and Table 7 depict the septic complication data. Twice as many TPN as TEN patients developed one or more in-

TABLE 7. *Patients With Postoperative Septic Complications by Surgery/Injury Type, Phase II Meta-Analysis (Including Dropouts)*

	Blunt Trauma		Penetrating Trauma		Nontrauma Surgery		Total Patients	
Complication	TEN (n = 48)	TPN (n = 44)	TEN (n = 38)	TPN (n = 40)	TEN (n = 32)	TPN (n = 28)	TEN (n = 118)	TPN (n = 112)
Abdominal abscess	2	1	2	6	1	0	5	7
Pneumonia	4	10	1	2	1	3	6	15
Wound infection	0	2	3	1	1	0	4	3
Bacteremia	1	4	0	1	1	0	2	5
Urinary tract infection	1	1	0	1	0	1	1	3
Catheter sepsis	0	4	0	1	0	2	0	7
Other	5	4	1	1	0	1	6	6
Total events	13	26	7	13	4	7	24	46
Number of patients	10	22	6	11	3	6	19	39
Per cent patients	21	50*,†	16	27.5	9	21	1	35*,†

Other infections included clinical sepsis in eight, meningitis, empyema, sinusitis, and not specified in one.

* p < 0.05 for all patients.

† p < 0.05, excluding patients with line sepsis (incidence of infections for total patients, p = 0.03; all trauma patients, p = 0.04; and blunt trauma patients, p < 0.05).

TEN, total enteral nutrition; TPN, total parenteral nutrition.

fections (TEN, 16%; TPN, 35%; p = 0.01) and there was no difference in the number of infectious complications per patient. The most significant differences in the number of patients with septic complications between subgroups were observed among all trauma (*i.e.*, blunt and penetrating) patients (p = 0.02) and among blunt trauma patients (p = 0.02). In the penetrating trauma subgroup, nearly twice the number of TPN as TEN patients developed infections; however, this difference was not statistically significant. No statistically notable difference in septic complications was seen in the nontrauma subgroup.

Because differences between TEN and TPN groups in septic complications could have been due to catheter sepsis, a second analysis of septic complications was performed that excluded patients with catheter sepsis. The seven episodes of catheter sepsis occurred in seven TPN patients. A significant difference between groups in the number of patients with septic complications remained when catheter sepsis patients were excluded from the analysis in (1) all patients combined (TPN, 29% *versus* TEN, 16%; p = 0.03), (2) all trauma patients (TPN, 33% *versus* TEN = 19%; p = 0.04), and (3) blunt trauma patients (TPN, 41% *versus* TEN, 21%; p = < 0.05).

Phase II meta-analysis also examined 10-day and 30-day mortality rates, length of hospital stay, and cost, but no significant differences between treatment groups were noted. Six (5%) TEN and seven (6%) TPN patients died during the first 10 days after entering the study (p = 0.78); five in each group were blunt trauma patients. At 30 days, eight (7%) TEN and 11 (10%) TPN patients had died; seven of the patients in each group were blunt trauma patients (p = 0.48). Only patients in the penetrating trauma group experienced significantly different lengths of hospital stay (TEN, 17 days; TPN, 22 days; p = 0.05) and ICU stay (TEN, 4.4 days; TPN, 7.3 days; p = 0.04). Total hospital cost data were available from only half of the sites and could not be combined because of extreme heterogeneity.

Discussion

Nutritional support has, by convention, been delayed for 5 to 7 days after surgery in the previously well-nourished hospitalized patient; TPN then may be initiated if the patient is intolerant of enteral intake.[35] There is an emerging consensus, however, that early (*i.e.*, within 48 hours) nutritional support benefits high-risk surgical patients.[1-8] Major injury or surgery induce a hypermetabolic, catabolic state in which, if not supported by exogenous substrates, excessive skeletal muscle proteolysis occurs, followed by depletion of crucial visceral and circulating proteins.[4,36,37] Clinical and basic research have confirmed that acute protein malnutrition impairs wound healing, vital organ function, and immunocompetence.[7,38-42] Indeed, this is the rationale for providing early nutritional support; but determining who the appropriate candidates are and what the preferred route of substrate delivery is have been difficult issues to resolve. Prospective, randomized, controlled trials have been the gold standard for assessing these questions. Unfortunately, clinical nutrition research is not well suited for this methodology.[43,44] By necessity, nutritional PRCTs are frequently open label, and therefore, with the exception of measuring a definitive end point (*e.g.*, death), study outcome indices are vulnerable to biased interpretation. Additionally, randomization of small numbers of patients has not adequately controlled the confounding variables present in complex patient scenarios. Therefore, strict inclusion/exclusion criteria are necessary but can severely limit patient enrollment. Typically a single institution does not have the patient volume necessary for timely completion of a large study and, even when well designed, the resulting small PRCTs are prone to generate misleading conclusions by type I (false-positive) or type II (false-negative) statistical error. Multicenter trials are viable alternatives but are pragmatically difficult to organize and require substantial funding.

In the past decade, meta-analysis has become a popular alternative to analyze combined PRCTs.[45-47] Meta-analysis is a statistical method for combining data from multiple protocols to provide evidence of statistical significance overall where individual study results are inconclusive.[30,31] Meta-analysis has typically been used to evaluate conflicting published reports. An extensive search is usually done to identify all published and unpublished trials in the given area of interest. These studies are then graded for quality, and only well-designed trials are included. This meta-analysis combined data from eight studies using similar protocols, conducted primarily to assess the nutritional equivalence of the same enteral formula compared with nutritionally similar TPN solutions. In each study, complications were prospectively recorded to monitor safety and feasibility. The original intent was to combine these trials as a multicenter experience, but variability of individual protocol implementation (*e.g.*, entry criteria, timing of measurements, TPN composition, etc.) precluded this type of data pooling. By using meta-analysis, these data were rigorously evaluated for combinability, and sufficient patient numbers (statistical power) were obtained to adequately assess whether TEN was associated with decreased septic complications. After the fact, a literature search disclosed no other trial that randomized high-risk surgical patients to early postoperative enteral feeding with an elemental enteral formula *versus* TPN that adequately addressed septic complications as a study end point.

The primary strength of this meta-analysis was negligible heterogeneity across and within studies. Additionally, dissimilar patients, variable composition and dosing of

nutritional support, and different methods of measuring outcome, which have been major obstacles of other nutrition-related meta-analyses, were not issues in this meta-analysis.[45-47] Furthermore, similar septic complication results were obtained in both the phase I meta-analysis of group-averaged data and in the phase II meta-analysis of individual patient data when dropouts were included. Consistency of individual study results, phase I results, and phase II results strengthened this observation, a technique referred to as sensitivity analysis.[31] Moreover, the observation of decreased septic complications in the TEN group, made in the subgroup analyses, were similar to the overall analysis and fit with our understanding of these patient types. The blunt trauma patients fed TEN experienced the most significant reduction in septic complications. This largest subgroup was at greatest risk of nosocomial pneumonias because major blunt trauma not only adversely affects immune function, but multiple injuries impose prolonged immobilization; in other words, the "horizontal crucifix" position as described by Border et al.,[5] which promotes nosocomial pneumonia.[5,48,49] The only potential confounding variable identified in this meta-analysis was that mean ATI was higher in penetrating trauma patients receiving TPN. Because each study in this meta-analysis was a PRCT, no specific attempts were made to place patients with higher ATIs into this TPN group. Randomization simply failed to control this variable. The TPN and TEN penetrating trauma subgroups, however, had similar ISSs. Moreover, there was a trend toward reduced sepsis (as with blunt trauma) with early enteral feeding. An after-the-fact power analysis indicated that the number of penetrating trauma patients would need to be doubled to demonstrate a statistically significant difference. More penetrating than blunt trauma patients would be required because it is harder to prove statistical significance for the observed 15% difference (15% TEN *versus* 30% TPN) than to prove significance for the 25% difference (25% *versus* 50% TPN) seen in the blunt trauma group. In sum, these findings suggest that the penetrating subgroup contributed to the overall observation of reduced septic morbidity rate with enteral feeding, and possibly, if a greater number of patients had been enrolled into the penetrating trauma subgroup, a balance in ATI scores might have been achieved, and a significant difference in group septic complications might have been observed. In contrast, the nontrauma patients had such a low incidence of septic complications that it would be quite difficult to discern a statistical difference in septic outcome. Thus the lack of statistically significant differences in the penetrating subgroup may be explained by inadequate sample size. In contrast, the nontrauma patients had such a low incidence of septic complications that differences in septic outcome were difficult to discern.

The superiority of TEN *versus* TPN in critically ill patients, assessed by traditional endpoints, is an unresolved issue. Total enteral nutrition is cheaper and safer, but TPN is easier to administer.[1] This meta-analysis, however, as well as other comparative trials, have shown that roughly 85% of high-risk surgical patients tolerate early postoperative enteral nutrition.[10,17] Although TPN can be advanced more rapidly, this is accompanied by greater nitrogen excretion. Piccone et al.[18] demonstrated the same nitrogen-sparing effect when delivering TPN by the portal vein. In this meta-analysis, nitrogen balance data consistently favored the TPN group; however, similar improvements in nutritional protein markers (total protein, albumin, transferrin) of both groups were observed (treatment failures included), indicating comparable nutritional repletion. Total parenteral nutrition patients also gained more weight. In part, this may be due to high TPN solution osmolality, which tends to promote water retention. Additionally, in comparative trials, McArdle et al.[16] and others have shown significant hyperglycemia in the face of high insulin levels in TPN patients, whereas TEN patients had only mild elevations in glucose and insulin.[6,16] The greater weight gain seen with TPN thus may be due to high insulin levels, which promote fat deposition. Finally, studies that have tested immunologic function, a common means of assessing the impact of nutritional support, favor the enteral route.[13,14,21,26,27,50] Although sophisticated tests were not performed in most of these studies, the documentation of reduced septic complications with TEN suggests better immunocompetence. The inclusion of the measurement of immunologic function markers may be an important objective for future TEN *versus* TPN studies.

How enteral feeding reduces septic complications appears to be multifactorial, but the exact mechanisms are unclear. The first clinical suggestion came from Alexander and associates[2] in 1980. They noted that severely burned children (average burn size, 60%) randomized to a high-protein enteral diet *versus* a normal (low-protein) diet had better immunologic parameters, less bacteremic days, and significantly improved survival.[2] In 1985, Moore and Jones[50] reported the results of a PRCT of 75 trauma patients with an ATI > 15. The control group received the conventional therapy of that time: no nutritional support for 5 days and then, if intolerant to oral intake, high-nitrogen TPN (nonprotein calorie to nitrogen ratio = 133:1). The treatment group received a high-nitrogen elemental diet, delivered early after operation, by needle catheter jejunostomy. They noted that total lymphocyte counts were better maintained, and significantly fewer major septic complications (pneumonia and bacteremia) occurred in the TEN group (4% *versus* 26%). In more recent human comparisons of TEN and TPN, Meyer et al.[26] showed that TPN adversely affects neutrophil response, whereas Lowry et al.[27] observed that parenterally fed patients exhibit an exaggerated cytokine response to

an endotoxin challenge. In an animal model, Birkhahn and Renke[51] have also shown that TPN fails to maintain lymphocyte function when compared with enteral feeding. Other basic research convincingly supports the observation that TEN is associated with improved immune function when compared with TPN. Kudsk et al.[13,14] showed that enteral feeding compared with TPN, in both malnourished and well-nourished rats, improved survival to a standard *Escherichia coli* hemoglobin peritonitis. Similarly, in a rodent model, Alverdy et al.[21] documented that enteral feeding maintains normal biliary levels of secretory IgA (S-IgA), whereas TPN is associated with a precipitous fall in S-IgA biliary levels. S-IgA is the principal immunoglobulin produced in response to orally delivered antigens and prevents binding of endotoxins and microorganisms to the intestinal microvilli. Initial intestinal antigen processing occurs in Peyer's patches from where stimulated β cells then migrate to distant mucosal sites (eyes, oropharynx, bronchial tree, breasts) so that the same protective S-IgA response occurs with a secondary antigen challenge.

Although the gut appears to be an important effector organ for immunologic function in critical illness, recent research has focused on its barrier function. Transmural migration of viable GI tract organisms (bacterial translocation) was demonstrated experimentally 40 years ago.[52] Most recently, the animal models of Deitch et al.[22] and others have comprehensively addressed the factors that govern this phenomenon.[22,24,53] A variety of insults (shock, burns, endotoxin) can compromise gut mucosal integrity, allowing the egress of bacteria into the mesenteric lymph nodes (MLN) of experimental animals. This response can be amplified by a variety of environmental cofactors such as GI bacterial overgrowth, depressed cell-mediated immunity, starvation, and alterations in specific nutrients so that bacteria spread to spleen, liver, and systemic blood. Although these animal studies are logical, consistent, and compelling, clinical evidence of bacterial translocation is sparse. Rush et al.[54] sampled blood within 3 hours of admission in 50 acutely injured patients. Cultures were positive in 10 (56%) of the 18 patients with an initial systolic blood pressure <80 mmHg. Unfortunately, this gravely injured group of patients had little chance of developing late sepsis (13 of 18 died within 24 hours). Moore et al.[55] recently confirmed that one third of patients arriving moribund had positive blood cultures, but again two thirds exsanguinated promptly. Whether these bacteremias are of gut origin and whether they contribute to early death or are just an epiphenomenon of severe shock is not clear. The Denver General group has also conducted a prospective trial in which 20 severely injured patients with known risk factors for MOF had portal vein catheters placed for sequential blood sampling for up to 5 days after operation.[55] Only eight (2%) of the 212 portal vein blood cultures were positive; seven of the cultured organisms were presumed contaminants. The only positive systemic culture (total, 212) was *Staphylococcus aureus* on day 5, in a patient with concurrent *Staphylococcus* pneumonia. Twelve of these patients had intraoperative MLN sampling; four (25%) were culture positive. Although these findings do not exclude the lymphatics as an early route of gut bacterial translocation, the lack of positive systemic cultures suggests this is a well-contained process. Bacterial translocation to MLN is a complex issue. Wells et al.[56] propose that translocation is part of the normal antigen-sampling process of gut-associated lymphoid tissue. In an animal model, Wells and colleagues have shown that suppression of cell-mediated immunity does not in itself promote translocation, but does permit greater numbers of translocated bacteria to survive in the MLN.[56] Thus, early translocation may be well contained in the MLNs, whereas delayed translocation by disrupted mucosal barrier, induced by a number of environmental cofactors in an immunocompromised host, may allow for systemic spread of viable gut bacteria.

Although there is no direct clinical evidence to support this contention, the epidemiologic studies of Marshal et al.,[57] Border et al.,[5] and others strongly implicate the gut as the occult source of bacteremias found in late sepsis-related MOF.[5,55-59] Indeed, the analysis by Driks et al.[60] of various stress ulcer prophylaxis regimens, and the recent trial of selective decontamination of the gut by Blair et al., and the previous study of Moore and colleagues[9] addressing the optimal route of nutritional support documented significant reductions in nosocomial pneumonia rates attributed to various gut specific therapies.[9,60,61] Presumably, in the first study, normal gastric acidity, and in the second study, topical antibiotics, prevented digestive tract colonization by hospital-acquired bacteria that subsequently were aspirated into the compromised lung. Thus, the stage was set for pneumonia to develop. In the third study it is tempting to assume that enteral nutrition prevented systemic bacterial translocation by maintaining gut barrier function and enhancing immunity; it is plausible, however, that the observed decreased incidence of pneumonia with enteral feeding is simply due to maintenance of a normal gut flora. If mesenteric lymph nodes could be serially sampled, perhaps a bacteriologic surveillance study of TEN *versus* TPN patients could identify the prime route of dissemination (*i.e.*, aspiration or translocation). Likewise, comparative clinical trials of the above gut-specific therapies could be revealing, but obviously need to be quite large to discern a difference in pneumonia rates given the effectiveness of the various therapies alone. In sum, the available clinical data strongly implicate the gut as the source of bacteria found in late nosocomial infections, but whether bacterial translocation is the prime pathway for its dissemination is speculative.

In conclusion, this two-part meta-analysis evaluated the effect of route of substrate delivery on septic complication development. Both phases of the meta-analysis demonstrated that significantly fewer enterally fed patients experienced septic complications. The most significant septic complication differences were seen in the all trauma and the blunt trauma subgroups. This study showed that early postoperative enteral feeding is feasible in high-risk surgical patients and may be beneficial in reducing septic morbidity rates.

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References

1. Moore EE, Moore FA. Immediate enteral nutrition following multisystem trauma. J Am Coll Nutr 1991; 10:633–648.
2. Alexander JW, MacMillan BG, Stinnett JD, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg 1980; 192:505–517.
3. Wilmore DW, Smith RJ, O'Dwyer ST, et al. The gut: a central organ after surgical stress. Surgery 1988; 104:917–923.
4. Cerra FB. Hypermetabolism, organ failure, and metabolic support. Surgery 1987; 101:1–14.
5. Border JR, Hassett J, LaDuca J, et al. The gut origin septic states in blunt multiple trauma (ISS = 40) in the ICU. Ann Surg 1987; 206:427–448.
6. Page CP. The surgeon and gut maintenance. Am J Surg 1989; 158: 485–490.
7. Law NW, Ellis H. The effect of parenteral nutrition on the healing of abdominal wall wounds and colonic anastomoses in protein-malnourished rats. Surgery 1990; 107:449–454.
8. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg 1984; 200:297–310.
9. Moore FA, Moore EE, Jones TN, et al. TEN versus TPN following major abdominal trauma—reduced septic morbidity. J Trauma 1989; 29:916–923.
10. Adams S, Dellinger EP, Wertz MJ, et al. Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. J Trauma 1986; 26:882–891.
11. Bower RH, Talamini MA, Sax HC, et al. Postoperative enteral versus parenteral nutrition. Arch Surg 1986; 121:1040–1045.
12. Peterson VM, Moore EE, Jones TN, et al. Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic protein reprioritization. Surgery 1988; 104:199–207.
13. Kudsk KA, Carpenter G, Peterson S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with *E coli*-hemoglobin adjuvant peritonitis. J Surg Res 1981; 31:105–110.
14. Kudsk KA, Stone JM, Carpenter G, Sheldon GF. Enteral and parenteral feeding influences mortality after hemoglobin-*E. coli* peritonitis in normal rats. J Trauma 1983; 23:605–609.
15. Saito H, Trocki O, Alexander JW, et al. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. JPEN 1987; 11:1–7.
16. McArdle AH, Palmason C, Morency I, Brown RA. A rationale for enteral feeding as the preferable route for hyperalimentation. Surgery 1981; 90:616–23.
17. Jones TN, Moore FA, Moore EE, McCroskey BL. Gastrointestinal symptoms attributed to jejunostomy feeding after major abdominal trauma: a critical analysis. Crit Care Med 1989; 17:1146–1150.
18. Piccone VA, LeVeen HH, Glass P, et al. Prehepatic hyperalimentation. Surgery 1980; 87:263–270.
19. Lickley HLA, Track NS, Vranic M, Bury KD. Metabolic responses to enteral and parenteral nutrition. Am J Surg 1978; 135:172–176.
20. Enrione EB, Gelfand MJ, Morgan D, et al. The effects of rate and route of nutrient intake on protein metabolism. J Surg Res 1986; 40:320–325.
21. Alverdy J, Chi HS, Sheldon GF. The effect of parenteral nutrition on gastrointestinal immunity. Ann Surg 1985; 202:681–684.
22. Deitch EA, Winterton J, Li M, Berg R. The gut as a portal of entry for bacteremia. Ann Surg 1987; 205:681–692.
23. Souba WW, Smith RJ, Wilmore DW. Glutamine metabolism by the intestinal tract. JPEN 1985; 9:608–617.
24. Alverdy JC, Aoys E, Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. Surgery 1988; 104:185–190.
25. Burke DJ, Alverdy JC, Aoys E, Moss GS. Glutamine-supplemented total parenteral nutrition improves gut immune function. Arch Surg 1989; 124:1396–1399.
26. Meyer J, Yurt RW, Duhaney R. Differential neutrophil activation before and after endotoxin infusion in enterally versus parenterally fed volunteers. Surg Gynecol Obstet 1988; 167:501–509.
27. Lowry SF. The route of feeding influences injury responses. J Trauma 1990; 30:S10–S15.
28. Cerra FB, Shronts EP, Konstantinides NN, et al. Enteral feeding in sepsis: a prospective, randomized, double-blind trial. Surgery 1985; 98:632–639.
29. Cerra FB, McPherson JP, Konstantinides FN, et al. Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. Surgery 1988; 104:727–733.
30. Sacks HS, Berrier J, Reitman D, et al. Meta-analysis of randomized controlled trials. N Engl J Med 1987; 316:450–455.
31. L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987; 107:224–233.
32. Grubbs FE. Procedures for detecting outlying observations in samples. Technometrics 1969; 11:1–21.
33. SAS User's Guide: Statistics. Version 5 Edition. Cary: SAS Institute, Inc., 1985.
34. SAS/STAT Guide for Personal Computers. Version 6 Edition. Cary: SAS Institute, Inc., 1987.
35. A.S.P.E.N. Board of Directors: Guidelines for the Use of Enteral Nutrition in the Adult Patient. JPEN 1987; 11(5):435–439.
36. Border JR, Chenier R, McMenamy RH, et al. Multiple systems organ failure: muscle fuel deficit with visceral protein malnutrition. Surg Clin North Am 1976; 56:1147–1167.
37. Bessey PQ, Jiang Z, Johnson DJ, et al. Posttraumatic skeletal muscle proteolysis: the role of hormonal environment. World J Surg 1989; 13:465–470.
38. Law DK, Dudrick SJ, Abdow NI. Immunocompetence of patients with protein-calorie malnutrition. Ann Intern Med 1973; 79:545–550.
39. Abel RM, Grimes JB, Alonso D, et al. Adverse hemodynamic and ultra structural changes in dog hearts subjected to protein-calorie malnutrition. Am Heart J 1979; 97:733–744.
40. Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 1982; 126:5–8.
41. Clark RM. The time-course of changes in mucosal architecture and epithelial cell production and cell shedding in the small intestine of the rat after fasting. J Anat 1975; 120:321–327.
42. Drabik MD, Schnure FC, Mok KT, et al. Effect of protein depletion and short-term parenteral refeeding on the host response to interleukin 1 administration. J Clin Lab Med 1987; 109:509–516.
43. Horwitz RI. Complexity and contradiction in clinical trial research. Am J Med 1987; 82:498–510.
44. Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. N Engl J Med 1978; 299:690–694.

45. Detsky AS, Baker JP, O'Rourke K, Goel V. Perioperative parenteral nutrition: a meta-analysis. Ann Intern Med 1987; 107:195–203.
46. Naylor CD, Detsky AS, O'Rourke K, Fonberg E. Does treatment with essential amino acids and hypertonic glucose improve survival in acute renal failure?: a meta-analysis. Ren Fail 1987; 10: 141–152.
47. Naylor CD, O'Rourke K, Detsky AS, Baker JP. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy: a meta-analysis. Gastroenterology 1989; 97:1033–1042.
48. Moore FA, Peterson VM, Moore EE, et al. Inadequate granulopoiesis after major torso trauma: a hematopoietic regulatory paradox. Surgery 1990; 108:667–675.
49. Christou NV, McLean APH, Meakins JL. Host defense in blunt trauma: interrelationships of kinetics of anergy and depressed neutrophil function, nutritional status and sepsis, J Trauma 1980; 20:833–841.
50. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: a prospective randomized study. J Trauma 1986; 26:874–881.
51. Birkhahn RH, Renke CM. Immune response and leucine oxidation in oral and intravenous fed rats. Am J Clin Nutr 1984; 39:45–53.
52. Schweinberg FR, Seligman AM, Fine J. Transmural migration of intestinal bacteria. N Engl J Med 1950; 242:747–751.
53. Deitch EA. Does the gut protect or injure patients in the ICU? Perspectives in Critical Care 1988; 1:1–24.
54. Rush BF, Sori AJ, Murphy TF, et al. Endotoxemia and bacteremia during hemmorhagic shock. Ann Surg 1988; 207:549–554.
55. Moore FA, Moore EE, Poggetti R, et al. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. J Trauma 1991; 31:629–635.
56. Wells CL, Maddaus MA, Simmons RL. Proposed mechanisms for the translocation of intestinal bacteria. Rev Infect Dis 1988; 10: 958–979.
57. Marshall JC, Christou NV, Horn R, Meakins JL. The microbiology of multiple organ failure. Arch Surg 1988; 123:309–315.
58. Goris RJA, Boekhorst TPA, Nuytinck JKS, Gimbrere JSF. Multiple organ failure, generalized autodestructive inflammation? Arch Surg 1985; 120:1109–1115.
59. Fry DE, Pearlstein L, Fulton RL, Polk HC. Multiple system organ failure. Arch Surg 1980; 115:136–140.
60. Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 1987; 317:1376–1382.
61. Blair PHB, Rowlands BJ, Lowry K, et al. Selective decontamination of the digestive tract (SDD): a stratified randomized prospective study in a mixed ICU. Surgery 1991; 110:303–310.